PATENT
ELG Docket No. IPJ01-001-US

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Inventor/s:	Stephen A. Boppart *et al.*
Serial No.:	10/753,972
Filing Date:	January 8, 2004
Title:	MULTI-FUNCTIONAL PLASMON RESONANT CONTRAST AGENTS FOR OPTICAL COHERENCE TOMOGRAPHY
Examiner:	Nasir Shahrestani
Group Art Unit:	3737

M.S. – Appeal Brief
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

APPELLANT'S BRIEF IN SUPPORT OF THE APPEAL TO THE BOARD OF PATENT APPEALS AND INTERFERENCES

TABLE OF CONTENTS

I. REAL PARTY IN INTEREST

The real party in interest is Purdue Research Foundation and the Board of Trustees of the University of Illinois.

II. RELATED APPEALS AND INTERFERENCES

There are no other related appeals or interferences.

III. STATUS OF CLAIMS

Pending claims 1-3, 7-26, and 31-39 have been finally rejected and are appealed. Claims 4-6, 27-30 and 40 have been cancelled.

IV. STATUS OF AMENDMENTS

Appellants filed an amendment to the claims on April 2, 2008, which was not entered by the Examiner. Applicants then filed an amendment to the claims on July 1, 2008, which was entered.

V. SUMMARY OF CLAIMED SUBJECT MATTER

Independent claim 1 provides a method of forming an image of a sample. (Specification, paragraph [0098]) The method comprises forming an image of a mixture, by exposing the mixture to electromagnetic radiation. (Specification, paragraph [0046]) The mixture comprises the sample and plasmon-resonant nanoparticles. (Specification, paragraph [0046]) The electromagnetic radiation is in

the frequency range of infra-red to ultraviolet light. (Specification, paragraph [0046]) The plasmon-resonant nanoparticles are anisotropic metallic nanoparticles. (Specification, paragraph [0046])

Independent Claim 19 provides a method of destroying tissue, comprising administering metallic anisotropic nanoparticles to the tissue to form a mixture, and subjecting the mixture to electromagnetic radiation. (Specification, paragraph [0046])

Independent Claim 22 provides, in a method of forming an image by optical coherence tomography, including exposing a patient to electromagnetic radiation, collecting reflected electromagnetic radiation, and forming an image from the collected electromagnetic radiation, the improvement comprising administering anisotropic metallic nanoparticles to a patient to enhance contrast of the image. (Specification, paragraph [0046]) The anisotropic metallic nanoparticles are gold nanorods with a magnetic tip. (Specification, paragraph [0074])

Independent Claim 26 provides a method of forming an image of a sample. The method comprises forming an image of a mixture, by exposing the mixture to electromagnetic radiation. (Specification, paragraph [0046]) The mixture comprises the sample and anisotropic metallic nanoparticles and the metallic nanoparticles comprise at least one member selected from the group consisting of gold, silver and copper. (Specification, paragraph [0046])

VI. GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

The issues to be decided on this appeal are as follows:

1) Whether claims 1-3, 7-25, 26, and 31-39 may be rejected on the grounds of non-statutory obviousness-type double patenting over claims 1-25 of U.S. Patent No. 7,198,777.

2) Whether claims 1-3, 7-21 are obvious under 35 U.S.C. § 103(a) over Toublan *et al.* (NPL-"Magnetically-inducible optical contrast agents for optical coherence tomography").

3) Whether claims 22-25, 26, and 31-39 are obvious under 35 U.S.C. § 103(a) over Sokolov (US 2004/0023415) in view of Lee *et al.* (NPL-"Engineered Microsphere Contrast agents for Optical Coherence Tomography").

VII. ARGUMENT

When imaging biological tissues, it is often desirable to enhance the signals measured from specific structures. Contrast agents, which produce a strong emission or reflection signal, have been utilized in virtually every imaging modality including ultrasound, computed tomography, magnetic resonance imaging, and optical microscopy.

Optical coherence tomography (OCT) is an emerging high-resolution medical and biological imaging technology. OCT is analogous to ultrasound B-mode imaging

except reflections of low-coherence light are detected rather than sound. OCT detects changes in the backscattered amplitude and phase of light from structures in tissue. This imaging technique is attractive for medical imaging because it permits the imaging of tissue microstructure *in situ*, yielding micron-scale imaging resolution without the need for excision and histological processing. OCT can record structures such as cell membranes, nuclei, and other organelles based on morphology-dependent optical characteristics. Because OCT performs imaging using light, it has a one- to two-order-of-magnitude higher spatial resolution than ultrasound and does not require contact with tissue.

Despite the rapidly growing acceptance of OCT in biomedical imaging, there are presently few agents available for enhancing optical contrast. This is partly attributable to the use of near infra-red (NIR) wavelengths (>800 nm) that are typically employed in OCT, which are outside the range of most optically active materials.

The present invention makes use of the discovery that *anisotropic* metallic nanoparticles can be used to enhance the contrast in analyses and imaging techniques that use electromagnetic radiation, particularly those techniques which use radiation in the frequency range of infrared to ultraviolet, such as optical coherence tomography, light microscopy, holography, confocal microscopy, polarization microscopy, interference microscopy, multi-photon microscopy, and endoscopy. Moreover, metallic nanoparticles composed of gold, silver, and/or copper are particularly suited as contrast agents for OCT applications. *Anisotropic* metallic

nanoparticles possess superior plasmon-resonant characteristics and may be fabricated in bimetallic forms to permit their use in OCT applications using switchable magnetic and electric fields. An important feature of plasmon resonance is its high sensitivity to shape anisotropy: isolated spherical nanoparticles typically support a single resonance frequency, whereas anisotropic particles (rods, triangles, ellipsoids, etc.) will exhibit at least one additional plasmon mode. (See Specification at paragraph [0049]). The nanoparticles efficiently absorb the incident optical radiation and can also be used as hyperthermia agents, creating local thermal gradients that are sufficient to kill individual cells. These contrast agents can therefore be used simultaneously for the detection and imaging of targeted cells followed by hyperthermic ablation.

The Examiner has failed to establish a *prima facie* case of obviousness as a basis for rejection of the present claims. Applicants have defined the phrase "*plasmon-resonant nanoparticles*" in the specification as "metallic nanoparticles that have an extinction coefficient of at least $10^6 M^{-1} cm^{-1}$ at some frequency in the range of 10^{12} to 10^{17} Hz." (See Specification at paragraph [34]). The Examiner has failed to consider Applicants' definition of the phrase "*plasmon-resonant nanoparticles*" when examining the claims, nor has the Examiner provided an alternative definition for this term. Additionally, the Examiner has not shown that the references teach or suggest all elements of the claims, and the Examiner has failed to provide a valid reason to modify the references to provide the missing claim elements.

A. Claims 1-3, 6-25, 26, and 31-39 May NOT Be Rejected On The Grounds Of Non-Statutory Obviousness-Type Double Patenting Over Claims 1-25 Of U.S. Patent No. 7,198,777.

When properly considered, the provisional rejection of the pending claims under the judicially created doctrine of obviousness-type double patenting over claims 1-25 of U.S. Patent No. 7,198,777 (Boppart *et al.*) is improper and must be withdrawn. The present application and Boppart *et al.* are not commonly owned, and were not developed as part of a joint research agreement.

Applications having different inventive entities can only be rejected on the ground of double patenting when one of two conditions is met: a) the applications are commonly owned, or b) the claimed invention resulted from activities undertaken with the scope of a joint research agreement as defined in 35 U.S.C. § 103(c)(3). See MPEP §§ 804.03(I) and 804.03(II). The present application is, and always has been, jointly owned by the Board of Trustees of University of Illinois and by the Purdue Research Foundation. In contrast, Boppart *et al.* is owned solely by the Board of Trustees of University of Illinois. Thus, the applications are not "commonly owned" as defined in MPEP § 706.02(l)(2). In addition, the inventions claimed in the present application and in Boppart *et al.* were not made by or on behalf of parties to a joint research agreement that was in effect on or before the date the claimed inventions were made. Thus, the applications do not meet the requirements for a rejection based on obviousness-type double patenting.

Furthermore, a complete *prima facie* case of obviousness-type double patenting over the claims of Boppart *et al.* has not been presented, since the claim element "wherein the mixture comprises the sample and *anisotropic* metallic nanoparticles" of the pending claims is not found in the claims of Boppart *et al.*, nor obvious over the claims of Boppart *et al.* The only reasoning provided by the Office for applying the double patenting rejection is that:

> … [a]lthough the conflicting claims are not identical, they are not patentably distinct from each other because they represent obvious alternative variations and groupings of the patented claims. (Office Action dated December 31, 2007, page 3.)

However, independent claim 26 includes the claim element "wherein the mixture comprises the sample and *anisotropic* metallic nanoparticles", which is not present in the claims of Boppart *et al.* Thus, the claims of Boppart *et al.* cannot be fully-encompassed by the pending claims. Since all elements in the pending claims have not been considered, a *prima facie* case of obviousness-type double patenting has not been presented. (See MPEP § 2143.03.) Withdrawal of this rejection is respectfully requested.

B. Claims 1-3, 6-21 Are NOT Obvious Under 35 U.S.C. § 103(A) Over Toublan *Et al.* (NPL-"Magnetically-Inducible Optical Contrast Agents for Optical Coherence Tomography").

1. The Examiner Has Failed to Consider the Term "Plasmon-Resonant Nanoparticles" When Examining the Claims.

The Examiner has failed to properly consider the meaning of the phrase "plasmon-resonant nanoparticles" when examining the claims. Claim 1 of the present application includes forming an image of a mixture, by exposing the mixture to electromagnetic radiation. The mixture comprises the sample and *plasmon-resonant nanoparticles*, wherein the plasmon-resonant nanoparticles are anisotropic metallic nanoparticles. The electromagnetic radiation is in the frequency range of infra-red to ultraviolet light.

The specification explicitly defines the phrase "*plasmon-resonant nanoparticles*" as "metallic nanoparticles that have an extinction coefficient of at least $10^6 M^{-1} cm^{-1}$ at some frequency in the range of 10^{12} to 10^{17} Hz." (See Specification at paragraph [34].) "When the specification states the meaning that a term in the claim is intended to have, the claim is examined using that meaning, in order to achieve a complete exploration of the applicant's invention and its relation to the prior art. *In re Zletz*, 893 F.2d 319, 13 USPQ2d 1320 (Fed. Cir. 1989)." (M.P.E.P. 2173.05(a) "New Terminology," Section I.) Furthermore, "[w]here an explicit definition is provided by the applicant for a term, that definition will control interpretation of the term as it is

used in the claim. *Toro Co. v. White Consolidated Industries Inc.*, 199 F.3d 1295, 1301, 53 USPQ2d 1065, 1069 (Fed. Cir. 1999) (meaning of words used in a claim is not construed in a "lexicographic vacuum, but in the context of the specification and drawings")." (M.P.E.P. 2111.01 "Plain Meaning," Section IV.)

The Examiner has refused to consider Applicants definition of the phrase "plasmon-resonant nanoparticles." (See Advisory Action dated September 16, 2008, page 2.) The Examiner has stated that the phrase "plasmon-resonant nanoparticle" is only referred to, in paragraph [34] of the specification, but not defined. (*Id.*) The Examiner then states that the term "refers" is distinctive from the term "defined" and hence the term "plasmon-resonant" is open to interpretation. (*Id.*) When Applicants used the term "refers to" in defining the phrase "plasmon-resonant nanoparticles," Applicants were clearly defining the phrase "plasmon-resonant nanoparticles" since the phrase appeared in the Definitions section of the present application and the phrase was followed by its explicit definition. (See Specification at paragraphs [21] and [34].) The Examiner must use the explicit definition provided by Applicants when examining the claims, since that definition controls interpretation of the phrase "plasmon-resonant nanoparticles" as it is used in claim 1. Yet, the Examiner has failed to do so by his own admission. (See Advisory Action dated September 16, 2008, page 2.)

Additionally, the Examiner has failed to provide an alternative meaning or even consider the phrase "plasmon-resonant nanoparticles." "All words in a claim must be considered in judging the patentability of that claim against the prior art." (In

re Wilson, 424 F.2d 1382, 1385, 165 USPQ 494, 496 (CCPA 1970).) In the present application, the Examiner has simply rejected the claims without considering Applicants' definition of the phrase "*plasmon-resonant nanoparticles.*" Moreover, the Examiner has failed to provide an alternative definition for or even mention the phrase "*plasmon-resonant nanoparticles*" at all. As a result, Applicants maintain that the Examiner has failed to properly consider the phrase "plasmon resonant nanoparticles."

2. The Applied Reference Does Not Describe "Anisotropic Nanoparticles."

When considered in its entirety, the applied reference, Toublan *et al.* does not disclose anisotropic nanoparticles. Toublan *et al.* is directed to contrast agents in medical and biological imaging to enhance the sensitivity of detection and improve the diagnostic ability of imaging techniques. (See Toublan *et al.*, first paragraph) Toublan *et al.* further discusses using *microspheres* of 0.5 to 5 microns in diameter with a 50 Å thick protein shell as optical contrast agents. (See Toublan *et al.*, fifth paragraph) The microspheres can be filled with scattering substances such as melanin or gold. (*Id.*)

Claim 1 of the present application includes forming an image of a mixture, the mixture comprises the sample and plasmon-resonant nanoparticles, wherein the plasmon-resonant nanoparticles are *anisotropic* metallic nanoparticles. Scattering substances such as melanin or gold are not necessarily anisotropic nanoparticles, since

being an anisotropic nanoparticle depends on not only the size of the particle, but the particle's *shape* as well. (See Specification, Paragraphs [0031] and [0049])

The Examiner maintains that Toublan *et al.* teaches that the material within the microspheres may be of varying shapes and sizes, and points to FIG. 1 for support of this proposition. (Office Action dated December 31, 2007, page 4.) While FIG. 1 of Toublan *et al.* illustrates microspheres of varying shapes and sizes, it is silent regarding the shape of the material within the microspheres and therefore does not teach that the material within the microspheres is anisotropic nanoparticles. Additionally, Toublan *et al.* is completely silent as to whether or not the material within the microspheres is plasmon resonant. Accordingly, Toublan *et al.* is completely silent as to disclosing a mixture which comprises the sample and plasmon-resonant nanoparticles, wherein the plasmon-resonant nanoparticles are anisotropic metallic nanoparticles.

C. Claims 22-25, 26, and 31-39 Are NOT Obvious Under 35 U.S.C. § 103(A) Over Sokolov (US 2004/0023415) in View of Lee *et al.* (NPL-"Engineered Microsphere Contrast Agents for Optical Coherence Tomography").

1. The Applied References Do Not Disclose "Gold Nanorods with Magnetic Tips."

When considered in their entirety, the applied references do not disclose gold nanorods with magnetic tips. Claim 22 of the present invention addresses the

problem of forming an image by optical coherence tomography, including exposing a patient to electromagnetic radiation, collecting reflected electromagnetic radiation, and forming an image from the collected electromagnetic radiation. The improvement comprises administering anisotropic metallic nanoparticles to a patient to enhance contrast of the image, wherein the anisotropic metallic nanoparticles are *gold nanorods* with a *magnetic tip*.

Sokolov discloses methods and apparatuses for using biospecific contrast agents to enhance the imaging of cells. (See Sokolov, paragraph [0039].) Described are metal nanoparticles and quantum dots attached to probe molecules with a high affinity to a specific biomarker on the surface of pre-cancerous and cancerous cells, to enhance the imaging of those cells. (See Sokolov, paragraph [0040].) Sokolov also discloses that colloidal gold and silver nanoparticles exhibit beautiful and intense colors in the visible spectral region. (See Sokolov, paragraph [0071].). Sokolov then states that it is believed that these colors are the result of excitation of surface plasmon resonances in the metal particles and are extremely sensitive to particles' sizes, shapes, and aggregation state; dielectric properties of the surrounding medium; adsorption of ions on the surface of the particles; etc. (*Id.*)

Lee *et al.* describes engineered microsphere contrast agents for optical coherence tomography. The contrast agents are microspheres 0.2 to 15 microns in diameter with an approximately 50 nm thick protein shell. (See Lee *et al.*, paragraph 2.) The microspheres are designed to incorporate in their shells and encapsulate in

their cores a wide range of nanoparticles and materials that alter the local optical properties of the tissue. (*Id.*)

Sokolov fails to teach or suggest gold *nanorods* with a *magnetic tip*. There is no teaching or disclosure within Sokolov of using a nanorod at all, let alone a gold nanorod with a magnetic tip. Furthermore, Lee *et al.* fails to cure all of the deficiencies of Sokolov. As a result, Claims 22-40 are not anticipated by, or obvious in view of, the cited references, either alone or in combination.

2. The Examiner Fails to Provide a Supported Reason for Inherency.

The Examiner has failed to provide a reason to support his assertion that gold nanoparticles inherently have magnetic tips. The Examiner's reason is unsupported by the cited references and appears to be made entirely from the personal knowledge of the Examiner.

An Examiner may not rely upon unsupported opinions within the personal knowledge of the Examiner in order to support a rejection. As noted by the court in In re Ahlert, 424 F.2d 1088, 1091, 165 USPQ 418, 420 (CCPA 1970), the notice of facts beyond the record which may be taken by the examiner must be "capable of such instant and unquestionable demonstration as to defy dispute" (citing In re Knapp Monarch Co., 296 F.2d 230, 132 USPQ 6 (CCPA 1961)). Furthermore, "[i]t would not be appropriate for the examiner to take official notice of facts without citing a prior art reference where the facts asserted to be well known are not capable of instant and unquestionable demonstration as being well-known." (See MPEP, Rev. 6, Sept.

2007, Section 2144.03, page 2100-146). Moreover, "rejections on obviousness grounds cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness" (See In re Kahn, 441 F. 3d 977, 988 (CA Fed. 2006)).

"If applicant challenges a factual assertion as not properly officially noticed or not properly based upon common knowledge, the Examiner must support the finding with adequate evidence." (See MPEP, Rev. 6, Sept. 2007, Section 2144.03, Section C., page 2100-146). Additionally, 37 C.F.R. § 1.104(d)(2), specifies that "when a rejection is based on facts within the personal knowledge of an employee of the Patent Office, the data shall be as specific as possible and the reference *must be supported*, when called for by the applicant, by the affidavit of such employee."

The Examiner has made the following assertion which is not supported by evidence in the record, and is not properly based upon common knowledge: "the metallic particles [disclosed in Sokolov] can be that of gold nanoparticles having a magnetic tip, as is the *inherent* property of gold (emphasis added)." (See Office Action dated December 31, 2007, page 4 last paragraph to page 5 first paragraph.)

Applicants have challenged the Examiner's assertion, but the Examiner has provided no evidence, such as a reference or an affidavit, stating the basis for this assertion. (See Applicant's Response to Office Action dated July 1, 2008.) Since the Examiner has not provided a reference or an affidavit stating the basis for the

assertion, Applicants maintain that the Examiner has not met the evidentiary burden required to sustain this rejection.

VIII. CONCLUSION

For the foregoing reasons, the claim rejections applied by the Examiner are unsustainable. Appellant respectfully requests reversal of the Examiner's rejections.

Respectfully submitted,

David Rozenblat
Registration No. 47,044

Evan Law Group
600 West Jackson Blvd., Suite 625
Chicago, IL 60661
(312) 876-1400

IX. CLAIMS APPENDIX

1. (Previously Presented) A method of forming an image of a sample, comprising:

forming an image of a mixture, by exposing the mixture to electromagnetic radiation;

wherein the mixture comprises the sample and plasmon-resonant nanoparticles,

wherein the electromagnetic radiation is in the frequency range of infra-red to ultraviolet light, and

wherein the plasmon-resonant nanoparticles are anisotropic metallic nanoparticles.

2. (Original) The method of claim 1, wherein the forming of the image is by a method selected from the group consisting of optical coherence tomography, light microscopy, holography, confocal microscopy, polarization microscopy, interference microscopy, multi-photon microscopy, and endoscopy.

3. (Original) The method of claim 1, wherein the forming of the image is by optical coherence tomography.

4-6. (Cancelled)

7. (Previously Presented) The method of claim 1, wherein the anisotropic metallic nanoparticles comprise nanorods or nanotriangles.

8. (Previously Presented) The method of claim 1, wherein the anisotropic metallic nanoparticles comprise gold.

9. (Previously Presented) The method of claim 1, wherein the anisotropic metallic nanoparticles further comprise a surface modification.

10. (Previously Presented) The method of claim 1, wherein the anisotropic metallic nanoparticles comprise a magnetic metal.

11. (Original) The method of claim 10, wherein the magnetic metal comprises at least one member selected from the group consisting of nickel, cobalt, and iron.

12. (Original) The method of claim 9, wherein the surface modification comprises a cross-linked surfactant shell.

13. (Original) The method of claim 12, wherein the cross-linked surfactant shell comprises at least one member selected from the group consisting of cross-linked resorcinarenes and cross-linked olefin.

14. (Original) The method of claim 13, further comprising, attached to the cross-linked surfactant shell, at least one member selected from the group consisting of folate, a monoclonal antibody, and a membrane receptor ligand.

15. (Original) The method of claim 10, further comprising exposing the mixture to a magnetic field.

16. (Original) The method of claim 10, further comprising exposing the mixture to an electric field.

17. (Original) The method of claim 2, wherein the sample is a patient.

18. (Original) The method of claim 3, wherein the sample is a human patient.

19. (Original) A method of destroying tissue, comprising:

administering metallic anisotropic nanoparticles to the tissue to form a mixture; and

subjecting the mixture to electromagnetic radiation.

20. (Original) The method of claim 19, wherein the electromagnetic radiation is in the frequency range of infra-red to ultraviolet light.

21. (Original) The method of claim 19, wherein the tissue is human.

22. (Original) In a method of forming an image by optical coherence tomography, including exposing a patient to electromagnetic radiation, collecting reflected electromagnetic radiation, and forming an image from the collected electromagnetic radiation, the improvement comprising administering anisotropic metallic nanoparticles to a patient to enhance contrast of the image,

wherein the anisotropic metallic nanoparticles are gold nanorods with a magnetic tip.

23. (Original) The method of claim 22, wherein the gold nanorods have an aspect ratio of 4:1 to 10:1 and a diameter of 10 nm to 100 nm.

24. (Original) The method of claim 22, wherein the magnetic tip is one metal selected from the group consisting of cobalt, nickel, and iron.

25. (Original) The method of claim 22, wherein the patient is a human.

26. (Currently Amended) A method of forming an image of a sample, comprising:

forming an image of a mixture, by exposing the mixture to electromagnetic radiation;

wherein the mixture comprises the sample and anisotropic metallic nanoparticles and the metallic nanoparticles comprise at least one member selected from the group consisting of gold, silver and copper.

27-30. (Cancelled)

31. (Currently Amended) The method of claim 26[[30]], wherein the anisotropic metallic nanoparticles comprise nanorods or nanotriangles.

32. (Currently Amended) The method of claim 26[[30]], wherein the anisotropic metallic nanoparticles further comprise a surface modification.

33. (Original) The method of claim 32, wherein the surface modification comprises a cross-linked surfactant shell.

34. (Original) The method of claim 33, wherein the cross-linked surfactant shell comprises at least one member selected from the group consisting of cross-linked resorcinarenes and cross-linked olefin.

35. (Original) The method of claim 34, further comprising, attached to the cross-linked surfactant shell, at least one member selected from the group consisting of folate, a monoclonal antibody, and a membrane receptor ligand.

36. (Currently Amended) The method of claim 26[[30]], wherein the anisotropic metallic nanoparticles comprise a magnetic metal.

37. (Original) The method of claim 36, wherein the magnetic metal is nickel, cobalt, or iron.

38. (Original) The method of claim 37, further comprising exposing the mixture to a magnetic field.

39. (Original) The method of claim 37, further comprising exposing the mixture to an electric field.

40. (Cancelled)

X. EVIDENCE APPENDIX

None

XI. RELATED PROCEEDINGS APPENDIX

None